UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/945,391 | 08/31/2001 | Jallal Messadek | 31927 | 3208 |

7590 06/04/2003

HOVEY, WILLIAMS, TIMMONS & COLLINS
Suite 400
2405 Grand Boulevard
Kansas City, MO 64108

| EXAMINER |
|---|
| OSTRUP, CLINTON T |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1614 | 9 |

DATE MAILED: 06/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/945,391 | MESSADEK, JALLAL | |
| | Examiner | Art Unit | |
| | Clinton Ostrup | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *18-21 and 25-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,22-24 and 28-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-30* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1,8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

Claims 1-30 are pending in this application.

### *Priority*

Priority to International PCT Application Number PCT/BE00/00021, filed March 01, 2000, has been acknowledged.

### *Election/Restrictions*

Applicant's election without traverse of Group I claims 1-17, 22-24, and 28-30 in Paper No. 7 is acknowledged.

Claims 18-21 and 25-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7.

### *Oath/Declaration*

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> It does not identify the mailing or post office address of each inventor. A mailing or post office address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing or post office address should include the ZIP Code designation. The mailing or post office address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.

### *Claim Objections*

Claim12 is objected to because of the following informalities: "hemorrhage" is misspelled as "haemorrage". Appropriate correction is required.

***Claim R jections - 35 USC § 112, first paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating thrombosis, thrombo-embolic troubles, blood coagulation disorders, and thrombosis in a patient with hemorrhage risk, does not reasonably provide enablement for preventing thrombosis, thrombo-embolic troubles, blood coagulation disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The burden of enabling the prevention of thrombosis, thrombo-embolic troubles, blood coagulation disorders, and thrombosis in a patient with hemorrhage risk (i.e. the need for additional testing) would be greater than that of enabling a treatment for the thrombosis, thrombo-embolic troubles, blood coagulation disorders, and thrombosis in a patient with hemorrhage risk. In the instant case, the specification does not provide guidance as to how one skilled in the art would go about preventing thrombosis, thrombo-embolic troubles, blood coagulation disorders, and thrombosis in a patient with hemorrhage risk or how the patient could be kept from ever being susceptible to these ailments. Nor is there any guidance provided as to a specific protocol to be utilized in order to prove the efficacy of the presently claimed method in preventing thrombosis, thrombo-embolic troubles, blood coagulation disorders, and thrombosis in a patient with

hemorrhage risk. Specifically, it is highly unlikely, and the Office would require experimental evidence to a claim such as that of claim 1, which claims to prevent the thrombosis in a patient by simply administering, by any method, an amount of glycine betaine. The specification fails to enable one of ordinary skill in the art to practice and use the methods of instant claims 1-14.

The term "prevention" is synonymous with the term "curing", and both circumscribe methods of treatment having absolute success. Since absolute success is not reasonably possible with most diseases, especially ones having etiologies as complex/poorly characterized as thrombosis, thrombo-embolic troubles, blood coagulation disorders, and thrombosis in a patient with hemorrhage risk, the specification is viewed as lacking an adequate written description of same (indeed, it could not provide one). The examiner recommends replacing "prevention" with treatment of patients at increased risk to suffer from thrombosis, thrombo-embolic troubles, blood coagulation disorders, and thrombosis in a patient with risk of undergoing a hemorrhage.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,

7) the predictability of the art, and
8) the breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth hereinbelow.

1. The nature of the invention, state of the prior art, relative skill of those in the art, the predictability of the art

The claimed invention relates to the prevention of thrombosis, thrombo-embolic troubles, blood coagulation disorders, and thrombosis in a patient with hemorrhage risk.
The relative skill of those in the art is generally that of a PHD candidate or PHD.

2. The breadth of the claims

Claims 1-14 are very broad and inclusive of any and all methods of administration of glycine betaine to treat any and all forms of thrombosis.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for treating any and all forms of thrombosis other than and specific types of thrombo-embolic and haemostatic diseases of arterial or venous origin which are even more limited in the working examples.

4. The quantity of experimentation necessary

Applicant fails to provide guidance and information sufficient to allow the skilled artisan to ascertain how to absolutely cure (i.e. prevent) any and all forms of thrombosis by any form of administration of the claimed agent, glycine betaine. Testing would have to be conducted on each form of administration and on each form of thrombosis, with no expectation of success for the prevention of thrombosis, as claimed instantly.

Given the above facts, it is clear that the art to which the instant invention relates involves a relatively high degree of unpredictability.

***Claim Rejections - 35 USC § 112, second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "thrombo-embolic trouble" in claim 4 is a relative term which renders the claim indefinite. The phrase "thrombo-embolic trouble" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of "thrombo-embolic trouble" have not been defined by the claims or the specification, thus it is unclear what constitutes and/or what does not constitute "thrombo-embolic trouble" as claimed instantly in claims 4-6.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4-5, 7-8, 10-13, 15-16, 22-23, and 28-29 are rejected under 35 U.S.C. 102(a) as being anticipated by Mar et al., Betaine in wine: answer to the French paradox., Med Hypothesis, 1999 Nov; 53(5):383-5.

Instant claims 1-2, 4-5, 7-8, 10-13, 15-16, 22-23, and 28-29 have only one method step, the administration of a therapeutically effective amount of glycine betaine. Mar et al teach that drinking wine may be protective against ischemic heart disease and

the betaine in wine may be responsible for reducing homocysteine levels, high levels of which are an independent risk factor for heart disease. Therefore, the addition of betaine to wine, and the subsequent drinking of said wine, reads on the method steps of instant claims 1-2, 4-5, 7-8, 10-13, 15-16, 22-23, and 28-29.

Claims 7-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Salamone et al., Changes in blood coagulation in experimental subacute poisoning with p-chlorobenzene. The influence of some lipotropic factors, Folia Medica (Naples), 1960, 43, 259-66.

The reference teaches subacutely administering, to guinea pigs, a mixture of equal parts of p-dichlorobenzene (I) and olive oil, which produced hepatic steatosis and prolongation of blood coagulation by reduction of the activity of the prothrombin complex, esp. of factor VII, prothrombin, and thromboplastin. However, the simultaneous administration of betaine, choline, and vitamin B12 showed a marked protective effect. Therefore, the reference teaches the methods steps of instant claims 7-9 and specifically teaches glycine betaine as providing a treatment for blood coagulation disorders in a patient, as claimed instantly.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-15, 16-17, 22-24, and 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haussinger, 5880098 and further in view of Kalvinish et al., WO 97/06795.

Haussinger teaches that osmolytes such as betaine have a powerful capacity to maintain cellular integrity in specific cells and that an important aspect of the present invention is to use an effective amount of the osmolyte and a thrombolytic agent in combination for the manufacture of an agent capable of treating complications resulting from ischemmia, hypoxia, or oxidative stress. The Haussinger reference teaches that such an agent will especially be useful for treating complications related to myocardial infarction wherein the thrombolytic agent with a capacity to induce lysis of blood clots. The primary reference describes how osmolytes have an important potential in preventing vascular dysfunctions leading to impairments of the blood flow, vascular dysfunction and related diseases and claims a method of treating or preventing complications resulting from ischemia, hypoxia or oxidative stress. See: col. 2, line 53 - col. 5, line 33; col. 9, lines 15-30; and abstract.

Although the primary reference teaches using compositions comprising osmolytes, such as betaine, for the treatment of thrombosis, the lysing of blood clots, and blood flow disorders, the primary reference lacks the specific teaching of administering the betaine by subcutaneous injection.

Kalvinish et al. teach pharmaceutical compositions comprising gamma-butyrobetaine for oral, parenteral, subcutaneous, or rectal administration that provide treatment for blood circulatory disorders. See: page 2, Disclosure of the Invention and abstract.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to have modified the method of treating thrombosis, the lysing of blood clots, and blood flow disorders, using the compositions comprising betaine, as taught by Haussinger, by administering said compositions subcutaneously, as taught by Kalvinish et al, because of the reasonable expectation of obtaining a method treating blood flow disorders by a method which have been shown to be effective in the administration of other betaine containing compositions for the same purpose.

**Conclusion**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Clinton Ostrup whose telephone number is (703) 308-3627. The examiner can normally be reached on 8:00am - 4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on (703) 308-4725. The fax phone numbers for the organization where this application or proceeding is assigned are (703)

308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Clinton Ostrup
Examiner
Art Unit 1614

Frederick Krass
Primary Examiner
Art Unit 1614

June 2, 2003